Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 12, 13, 17-20, 24-32 and 34-37 are pending in the application, with 12, 34 and 36 being the independent claims. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Interview

Applicants wish to thank the Examiner for the personal interview of October 6, 2004, during which the issue of written descriptive support under 35 U.S.C. §112(1) was discussed. Additionally, Examiner Marschel suggested claim amendments to put the claims into condition for allowance.

II. Objection to the Specification

The Examiner has objected to the disclosure because of the following informalities: "1) The Figure 1 Brief Des. cites HBGF-1β whereas, in contrast, Figure 1 cites ECGF." (Paper No. 62904, page 14). Applicants submit herewith formal drawings which omit "ECGF" and eliminates this inconsistency. Thus, Applicants request that the Examiner reconsider and withdraw this objection.

The Examiner has also stated that, "the Figure 2 Brief Des. cites HBGF-1β or HBGF-1, whereas, in contrast, ECGF is cited in Figure 2." The Examiner went on to state that, "within the Figure 2 Brief Des. the growth factor is inconsistently cited as

HBGF-1β vs. HBGF-1." (Paper No. 62904, page 14). Based on the teachings in the specification, one of ordinary skill in the art would understand that the Figure should refer to "HBGF-1β" instead of "ECGF." Applicants have filed herewith an amended Figure 2 to correct this obvious error.

The Examiner has further objected to the specification because "HBGF-1 is cited in other Figure Brief Descriptions which confusingly may or may not be different from HBGF-1β." (Paper No. 62904, page 15). Applicants refer the Examiner to the specification at page 35, lines 9-17, which recites:

> As used herein, HBGF-1, which is also known to those of skill in the art by alternative names, such as endothelial cell growth factor (ECGF) and FGF-1, refers to any biologically active form of HBGF-1, including HBGF-1β, which is the precursor of HBGF-1α and other truncated forms, such as FGF. U.S. Patent No. 4,868,113 to Jaye *et al.*, herein incorporated by reference, sets forth the amino acid sequences of each form of HBGF. HBGF-1 thus includes any biologically active peptide, including precursors, truncated or other modified forms, or mutants thereof that exhibit the biological activities, or a subset thereof, of HBGF-1.

Applicants believe that this portion of the specification addresses the Examiner's concerns and explains why some citations are to HBGF-1 and some are to HBGF-1β. Thus, Applicants respectfully request that the Examiner reconsider and withdraw the objection.

The Examiner also objected to the disclosure because the heparin amounts in the Figure panels are given as "u/ml" whereas, in contrast, the Brief Des. cites "U/ml". (*See* Paper No. 62904, page 14.). Applicants submit that one of ordinary skill in the art would reasonably understand that the discrepancy is a minor typographical error. However,

solely to advance prosecution and not in acquiescence of the Examiner's objection, Applicants have amended the specification to obviate any confusion. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the objection.

III. Objection to the Title

The Examiner has objected to the title, stating that it is not descriptive. Applicants have amended the title and believe it is now clearly indicative of the invention to which the claims are directed. Applicants assert that this rejection has been overcome and respectfully request that Examiner withdraw this objection.

IV. Objections to the Drawings

The Examiner has objected to the drawings filed on June 7, 1995. Applicants have submitted formal drawings herewith and respectfully request that the Examiner withdraw this objection.

V. Rejections under 35 U.S.C. § 112(1)

Claims 12, 13, 17-20, 24-32 and 34-37 have been rejected under 35 U.S.C. §112(1), as failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

1. Written Description

a) Claims 12, 34 and 36

The Examiner has alleged that new matter was added to the claims via the phrase "said sustained period is greater than the period obtained due to simple diffusion kinetics," as is recited in claims 12, 34 and 36. The Examiner first asserted that the

supplements listed in claims 12, 34 and 36 would not be reasonably exemplified by only TGF-β2 practice because these supplements vary greatly compared to TGF-β2 in molecular properties (*See* Paper No. 62904, page 4). Applicants have amended claims 12, 34 and 36 to recite a supplement delivery system...wherein the supplement is delivered from the fibrin matrix for a sustained period...wherein said amount of said supplement is greater than the amount which is soluble in said fibrin matrix....and wherein said sustained period is greater than the period obtained when the amount of said supplement is soluble in said fibrin matrix.

An objective standard for determining compliance with the written description requirement of 35 U.S.C. §112, first paragraph, is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989), *see also* MPEP 2163.02 (2004). An applicant may show possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown by (1) a description of actual reduction to practice, or (2) by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or (3) by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. *See,* e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d

1398, 1406 (Fed. Cir. 1997); *Amgen v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 2001); *see also* MPEP 2163.02 (2004).

The example involving TGF-β2 is presented as one example of a supplement that has been shown to exhibit sustained release as recited in the pending claims. This example does not foreclose the rest of the supplements claimed in this application; it merely demonstrates one of the possible supplements. As was discussed at the interview of October 6, 2004, Applicants clearly contemplated and disclosed that, like TGF-β2, the other disclosed supplements could be delivered for a sustained period and thus Applicants had possession of the invention. For example, at page 22, lines 4-16 of the specification, Applicants state that poorly soluble drugs in general could be used for sustained delivery. Additionally, at page 23, lines 5-12, Applicants discuss supplementation and prolonged delivery of drugs generally. As discussed in the interview of October 6, 2004, the figures of the instant application and descriptions thereof also show specific examples of sustained delivery of supplement for a period longer than that obtained when the supplement is present in an amount that is soluble in said fibrin matrix.[1] Finally, all of the supplements recited in the instant independent claims are disclosed throughout the specification, thus Applicants assert that independent claims 12, 34 and 36 comply with the written description requirement of 35 U.S.C. §112.

The Examiner has also asserted that the specification fails to give written basis for the "greater than the period" limitation that is present in the last two lines of the instant independent claims. As noted in the response of August 23, 1999, the discussions

[1] *See* USSN 08/479,038; Figures: 23 (delivery of TET for 22 days); 24 (delivery of TET for 13 days); 25 (delivery of TET for 14 days); 28 (delivery of CIP, AMO, MET

in the personal interview of July 30, 1998, the subsequent telephone interviews and Dr. Friedman's December 16, 2002 Declaration under 37 C.F.R. §1.132 clearly establish that independent claims 12, 34 and 36 meet the requirements of 35 U.S.C. §112, first paragraph. Applicants have amended independent claims 12, 34 and 36 to replace this language with "greater than the period obtained when the amount of said supplement is soluble in said fibrin matrix," this language is believed to be adequately supported by the disclosure in the specification. As discussed in the interview of October 6, 2004, the figures showing sustained release of various drugs support this element. Specifically, Figure 32, for example, shows sustained release of 5-FU when loaded above the solubility limit as compared to 5-FU loaded in an amount that is soluble.

Further support for the "greater than the period" limitation in claims 12, 34 and 36 may be found in Examples 19, 20 and 21 of the specification, each of which describes a supplemented fibrin sealant that provides for sustained delivery of a supplement. An additional copy of Dr. Friedman's declaration is attached herein. Thus, Applicants assert that the specification as filed does provide adequate written basis for the "greater than the period" limitation in the instant independent claims.

The Examiner has also asserted that page 72 of the specification requires clot dissolution as the controlling mechanism for TGF-β2 delivery compared to simple diffusion kinetics (*See* Paper No. 62904, page 5). Amended claims 12, 34 and 36 recite that a fibrin matrix is formed and that the supplement is delivered from said fibrin matrix into the external environment of use for a sustained period. The Examiner has not cited any authority to support the assertion that the mechanism by which an invention

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for up to 42 days); 31(a)(delivery of AMP, CIP, TET for up to 42 days); 32 (sustained

functions must be recited in a claim. To the contrary, an inventor need not know how or why his or her invention works in order to obtain a patent. (*See Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989) (nothing that "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works.")

Thus, based on the proposed amendments and the discussions of the interview of October 6, 2004, Applicants assert that claims 12, 34 and 36 do not contain new matter and are in compliance with the written description requirement of 35 U.S.C. §112; therefore it is respectfully requested that this rejection be withdrawn.

b) Claims 12 and 34

The Examiner has rejected independent claims 12 and 34 under 35 U.S.C. §112, stating that these claims contain new matter. (*See* Paper No. 62904, page 5). Applicants respectfully traverse this rejection.

The Examiner has asserted that the citation in Example 21 at pages 107-109 describing supplementation of a tissue sealant above the solubility limit with taxol or paclitaxel does not support the phrase "said effective amount of said supplement is greater than the amount which is soluble in said fibrin matrix," thus claims 12 and 34 contain new matter. (*See Id.*, page 5). Specifically, he asserted that the citation in Example 21 is not directed to any supplement as included in the supplements listed in the presently pending claims and that the insolubility of taxol or paclitaxel is dependent on molecular weight of the supplement compared to that of the solvent. (*See Id.* at page 5).

Applicants point out that contrary to the Examiner's assertions, both taxol and

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delivery of 5-FU).

paclitaxel are examples of supplements included in the lists recited in claims 12 and 34. Those supplements fall within the categories of cell proliferation inhibiting compounds and chemotherapeutic drugs, as recited in claims 12 and 34.[2] Applicants clearly contemplated and disclosed that, like taxol, the other disclosed supplements could be delivered for a sustained period and thus had possession of the invention. For example, at page 22, lines 4-16 of the specification, Applicants state that poorly soluble drugs in general could be used for sustained delivery. The other supplements listed in the relevant claims are disclosed throughout the specification, as discussed in the interview of October 6, 2004.[3] Therefore, clearly Applicants contemplated and described the incorporation of any of the supplements recited in the claims. There is nothing in Example 21 or anywhere in the record that indicates that taxol and paclitaxel are the only two supplements which may be added in an amount above the solubility limit of the tissue sealant to practice the presently claimed supplement delivery system. Accordingly, this rejection cannot be maintained.

The Examiner also asserted that "the fibrin matrix content of taxol is based on its 'insolubility' and not on what is soluble therein as now claimed." (*Id.* p.6). The individual solubility of the exemplified supplements does not detract from the underlying premise that the chosen supplement must be loaded above its solubility limit in the tissue sealant. The supplements used in the claimed tissue sealants are present above their solubility limit, as described at page 104, lines 27-29, therefore the presently pending

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[2] *See* USSN 08/479,038; page 21, lines 8 to the end of the page.

[3] *See* USSN 08/479,038 Figures: 23 (delivery of TET for 22 days); 24 (delivery of TET for 13 days); 25 (delivery of TET for 14 days); 28 (delivery of CIP, AMO, MET for up to 42 days); 31(a)(delivery of AMP, CIP, TET for up to 42 days); 32 (sustained

claims are not broader than the specification. As discussed during the interview of October 6, 2004, the solubility limit of a supplement in a medium such as fibrin sealant may be readily determined by one of ordinary skill in the art without undue experimentation. Applicants assert that the specification provides sufficient support under 35 U.S.C. §112, first paragraph, for the phrase "said effective amount of said supplement is greater than the amount which is soluble in said fibrin matrix." Reconsideration and withdrawal of this rejection is respectfully requested.

2. Enablement

a) Claims 12, 13, 17-20, 24-32 and 34-37

The Examiner has rejected claims 12, 13, 17-20, 24-32 and 34-37 under 35 U.S.C. §112, first paragraph, asserting that the specification does not reasonably provide enablement for the practice of forming a fibrin matrix from a derivative or metabolite of fibrinogen in the presence of thrombin, Ca^{++}, and water. Solely to advance prosecution and not in acquiescence of the Examiner's rejections, Applicants have amended the relevant independent claims to omit this language. Thus, Applicants assert that this rejection has been overcome and reconsideration and withdrawal is respectfully requested.

VI. Rejections under 35 U.S.C. § 112(2)

1. Indefiniteness

a) Claims 12, 13, 17-20, 24-32 and 34-37

The Examiner has rejected claims 12, 13, 17-20, 24-32 and 34-37 under 35 U.S.C.§112, second paragraph, as being indefinite, asserting that the phrase "said

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delivery of 5-FU), showing various drugs loaded above their solubility limit in fibrin sealant.

derivative or metabolite thereof" in claim 12 lacks antecedent basis. Similarly, claim 36 also contains this phrase which allegedly lacks antecedent basis due to previous claim amendments that deleted the antecedent phrase. Solely to advance prosecution and not in acquiescence of the Examiner's rejection, Applicants have amended the relevant claims to omit this phrase. Reconsideration and withdrawal of this rejection is requested.

VII. Rejections under 35 U.S.C. § 102

1. Schlag et al.

a) Claims 12, 13, 18, 30-32, 34 and 36

The Examiner has rejected claims 12, 13, 18, 30-32, 34 and 36 under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Schlag *et al.* [Clinical Orthopaedic and Related Res. Vol. 227:269 (1988)] ("Schlag"). The Examiner has asserted that Schlag discloses a fibrin sealant containing fibrinogen, enhanced Factor XIII content and aprotinin as an inhibitor of fibrinolysis. (*See* Paper No. 62904, p.13). Applicants respectfully traverse this rejection.

Solely to advance prosecution and not in acquiescence of any of the Examiner's statements, Applicants have amended claims 12, 18 and 34-36 to recite compositions that are substantially free of protease inhibitors (such as aprotinin). Because all of the elements of the rejected claims are not met by the disclosure of Schlag, Applicants assert that these claims are not anticipated under §102(b).

Independent claims 12, 34 and 36 are also not obvious in view of Schlag, as this reference does not disclose or suggest all the elements of the presently pending claims. The Examiner has asserted that the disclosure of Schlag would be reasonably expected to contain the components of independent claims 12, 34 and 36. (*See* Paper No. 62904, p.

13). As noted above, claims 12, 18 and 34-36 have been amended to recite a supplement delivery system that is substantially free of protease inhibitors, but which delivers the supplement for a sustained period, wherein that sustained period is greater than the period obtained when the amount of said supplement is soluble in the fibrin matrix.

As is noted by the Examiner, the compositions disclosed by Schlag require a protease inhibitor (aprotinin). Further, Schlag states that antibiotics incorporated into fibrin clots are not sufficient to maintain adequate local drug concentrations for more than three days. (*See* Schlag, p.281).

In contrast, Figure 23 and the accompanying text of the instant specification show the extended *in vitro* release of supplement at varying concentrations for up to 22 days. As discussed in the interview of October 6, 2004, slide 11 of the December 16, 2002 declaration of Dr. Friedman evidences extended *in vivo* release of supplement for up to 42 days. Clearly, the sustained release as recited in the pending claims of the present invention was not suggested or even contemplated by Schlag. Thus, Applicants assert that the elements of claims 12, 13, 18, 30-32 34 and 36 have not been taught or suggested by Schlag, and respectfully request the reconsideration and withdrawal of the above rejections.

VIII. Rejections under 35 U.S.C. § 103

1. Marx in view of Popescu

The Examiner has rejected claims 17, 18, 25, 29-32 and 35-37 under 35 U.S.C. §103(a) as obvious over Marx [P/N 5,607,694] ("Marx"), taken in view of Popescu *et al.* [P/N 4,708,861] ("Popescu"). At page 9 of the outstanding Office Action, the Examiner noted that based on the earlier discussed new matter rejections, he is only considering the

effective filing date of June 7, 1995, and has not afforded the present application the proper priority date of March 12, 1993, as stated in the specification.[4]

As discussed in the interview of October 6, 2004, and as discussed above, Applicants respectfully assert that the new matter rejection under §112 has been overcome; thus the priority date of March 12, 1993 for the claims at issue is proper. Thus, Marx is not available as prior art under 35 U.S.C. §102, as its earliest claim to priority occurred after this date.

Popescu alone fails to disclose or teach the elements of the rejected claims in that it discloses sustained release compositions wherein the supplements are contained within liposomes inside gel compositions. (*See* Abstract of Popescu). First, Popescu does not teach or suggest incorporation of such liposomes in a tissue sealant as recited in the instant independent claims. There is no mention of fibrinogen anywhere in the cited reference. Further, the liposome-containing gels taught by Popescu would not be considered tissue sealants even without fibrin or fibrinogen.

Second, there is no discussion in Popescu about the concentration of supplement within the liposomes, and nothing that would indicate to one of ordinary skill in the art that said supplements are present within the liposomes at a level above the solubility limit, as required in the instant independent claims from which the presently rejected claims depend. Thus, Popescu does not teach or suggest this element of Applicant's presently claimed invention.

Finally, the Examiner has cited no authority for his assertion that entrapment of a supplement in a liposome as disclosed by Popescu may be reasonably interpreted to

[4] *See* USSN 08/031,164, filed March 12, 1993, now abandoned, at pages 12, 19-

disclose release of the supplements for a sustained period that is greater than the period obtained when the amount of supplement is an amount which is soluble in the fibrin matrix, as is required in the instant independent claims. Thus, Applicants assert that Marx is not prior art to the instant Application, and claims 17, 18, 25, 29-32 and 35-37 are not obvious over Popescu alone. Accordingly, the rejection for obviousness is misplaced. Reconsideration and withdrawal of this rejection is respectfully requested.

22, 31, 35, 36, 38, 71-77, 79-83, and Figures 22-27 and 30.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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